J. Perinat. Med.
4 (1976) 234

Comparative prognostic value of serum placental and tissue oxytocinase, alkaline phosphatase and its heat-stable fraction in pregnancy at neuroendocrinological risk

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Although enzyme assays, especially those for oxytocinases (CAP), heat-stable alkaline phosphatase (HSAP) and histaminase, are now thought to be well established diagnostic tools in so-called "placental insufficiency", opinions regarding their usefulness for monitoring high-risk pregnancies are still divided [11, 17, 23, 32]. Discrepant evaluations are probably due to different profiles of pregnant women studied and to the fact that only single enzyme assays and their correlations with results of hormonal studies are usually considered and are seldom compared with other enzymes. The purpose of this study was to compare the prognostic value of CAP and AP for endocrine monitoring of pregnancy at neuroendocrinological risk, i.e. pregnancy in women with neuroendocrinological disturbances diagnosed prior to the pregnancy under review [24]. We are not aware of any studies on the prognostic value of the aforementioned enzymes in cases of this sort.

Curriculum vitae

Prof. RUDOLF KLIMEK, *M.D., was born in Cracow (Poland) in 1932. Degree with distinction at the Cracow Medical Academy. Assistant at the Biochemical Department (Chairman: Prof.* B. SKARŻYŃSKI*) in 1954–1956. Since 1957 resident in obstetrics and gynecology at the I Clinic of Obstetrics and Gynecology in Cracow (Head: Prof.* S. SCHWARZ*). Assistant Professor (1964) and Professor of gynecology and obstetrics (1972). Director of the Institute of Gynecology and Obstetrics in 1969–1972. Now Chairman of the Clinic of Endocrinology of the Institute. He published on high-risk pregnancies, neuroendocrinology and clinical biochemistry and described a new entity – the hypothalamic post-pregnancy syndrome. Member of the International Society for Biochemical Pharmacology, International Society of Endocrinology, European Society for Clinical Investigation, American Association for the Advancement of Science and domestic societies.*

1 Case material and methods

The analysis concerns 364 pregnant women whose pregnancies were terminated by delivery and who had been hospitalized at the Clinic of Endocrinology of the Institute of Gynecology and Obstetrics of the Medical Academy in Cracow in the years 1971–1973. CAP was determined by TUPPY's method modified by KLIMEK [19] at pH = 7.9 (P-CAP) and pH = 6.0 (T-CAP) and AP and HSAP by KING and KING's method modified by HANSEN [14]. In these women, prior to the present pregnancy, ovarian disorders and/or sterility had been diagnosed as the cause of failure to become pregnant, and the majority (189 women) had been treated with hormones. Some of the women had been treated also during the

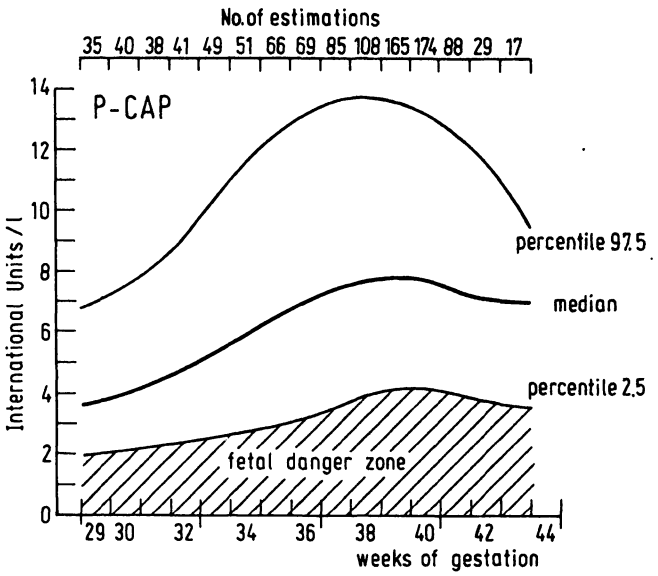

Fig. 1. Percentile curves and fetal danger zone of P-CAP.

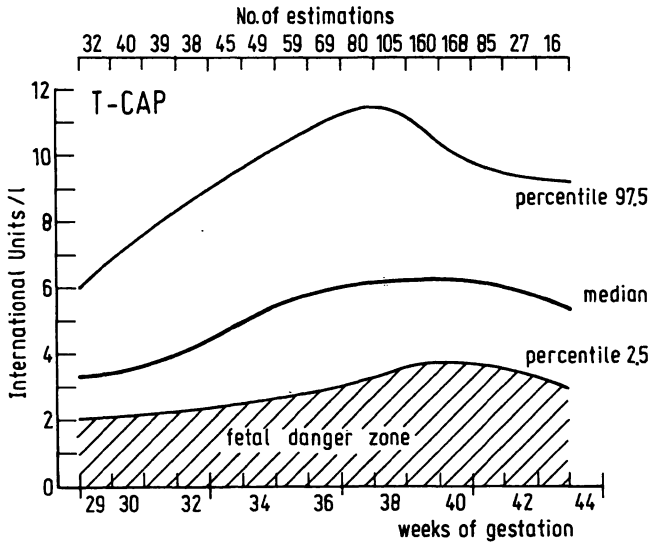

Fig. 2. Percentile curves and fetal danger zone of T-CAP.

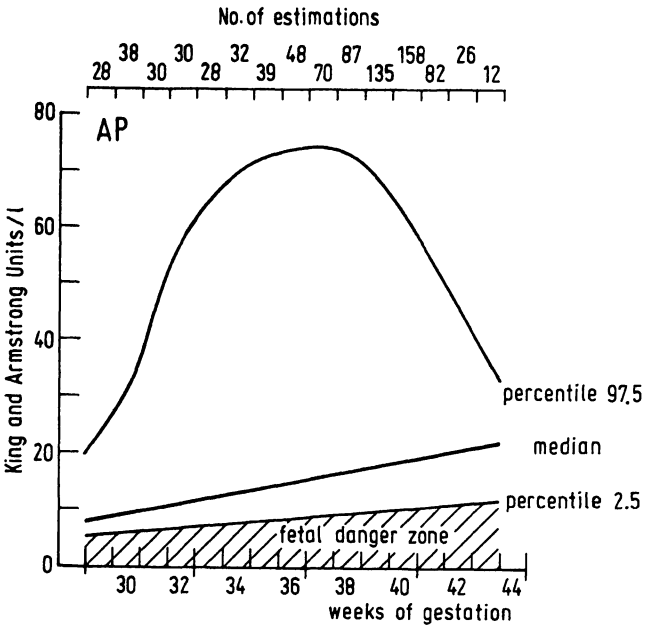

Fig. 3. Percentile curves and fetal danger zone of AP.

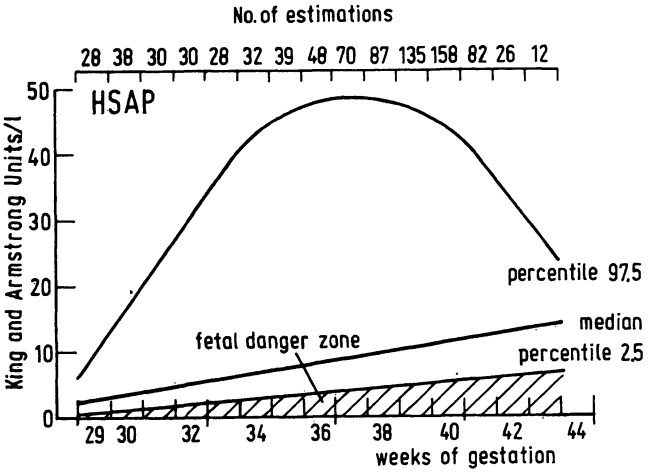

Fig. 4. Percentile curves and fetal danger zone of HSAP.

present pregnancy because of diabetes (9 women), cervical incompetence (10 women), gestosis (7 women), threatened abortion (59 women), feto-maternal immunization (3 women), or toxoplasmosis (25 women). Results of enzyme assays were compared at the 95 per cent confidence level, based on 2.5, 50.0 and 97.5 percentiles [15] with a series of 200 healthy pregnant women who delivered healthy children. Figs. 1–4 show the percentile curves, smoothed out graphically, from the calculated percentiles for each of the four enzyme assays. Absolute values of each enzyme activity and the curve profiles were evaluated separately.

1. Single values: Determinations were considered abnormal if at least one of the values was below the 2.5 percentile (in the fetal danger zone). In 364 pregnant women, P-CAP and T-CAP were calculated, and in 346 AP and HSAP.

2. Serial determinations: Enzyme assays were considered abnormal if two consecutive results showed a fall or remained at the same level. That is, only those women were included who had at least three enzyme assays during their pregnancy: P–CAP in 157 women, T-CAP in 149, and AP and HSAP in 134 women respectively.

Besides being evaluated according to normal or abnormal enzyme activity, the women were divided according to whether they gave birth to healthy or impaired neonates. An analysis was made of all impaired or dead neonates (perinatal mortality, congenital anomalies, one minute APGAR score below six, prematurity, intrauterine growth retardation, respiratory distress syndrome, postmature fetuses, and neonates with hemolytic disease), and separately against the rest of the material, perinatal mortality and low APGAR score were analyzed. Statistical analysis was made using the χ^2 test applying YATES correction, at one degree of freedom. In addition, sensitivity and specificity of the enzyme assays were evaluated. Sensitivity was defined as the percentage of women with abnormal enzyme assays among those who gave birth to impaired neonates. Specificity was defined by the percentage of women delivered of impaired neonates among all women with abnormal enzyme assays.

2 Results

The data in Tab. I indicate that a low P-CAP activity is valuable in forecasting the birth of an impaired or dead neonate, but not in predicting a low APGAR score. Half of the women with low activity of the enzyme will give birth to impaired children, but a value above percentile 2.5 does not exclude a threat to the infant because the sensitivity of this test is low (about 85 per cent of impaired neonates are not detected). A falling P-CAP curve also indicates general impairment of the neonate, but is not a prognostic sign of perinatal mortality or of a low APGAR score. Comparison with the single values shows that specificity of serial assays is somewhat lower. Only a third of women with abnormal profile of enzyme activity gives birth to impaired children. On the other hand, the sensitivity of this test is higher, nearly 40 per cent of mothers of future impaired infants show decreasing enzyme activity in the blood. Low T-CAP activity of the serum (Tab. II) also proved

Tab. I. Prognostic significance of the assays of serum placental oxytocinase activity.

No.: number of women delivered of impaired newborns
a: number of women delivered of impaired or dead babies with of normal enzyme values (false negative test)
b: number of women delivered of impaired or dead babies whose enzyme assays were abnormal (correct test)
c: number of women delivered of normal babies whose enzyme assays were normal (correct test)
d: number of women delivered of normal newborns with abnormal enzyme assay (false positive test)
χ^2: Chi-square test applying Yates correction
P: probability for one degree of freedom
N.S.:not significant

$$\text{Specificity} = \frac{b}{b+d} \times 100$$

$$\text{Sensitivity} = \frac{b}{a+b} \times 100.$$

	Condition	No.	a	b	c	d	χ^2	P	Specificity	Sensitivity
single assays	impaired or dead newborn	83	71	12	268	13	8.2064	< 0.01	48.00	14.46
	perinatal mortality	11	8	3	331	22	4.4601	< 0.05	12.00	27.27
	low Apgar score	28	24	4	315	21	1.5041	N.S.	16.00	14.27
serial assays	impaired or dead newborn	31	19	12	104	22	5.4280	< 0.02	35.29	38.71
	perinatal mortality	7	3	4	120	30	3.4693	N.S.	11.76	57.14
	low Apgar score	7	3	4	120	30	3.4693	N.S.	11.76	57.14

Tab. II. Prognostic significance of the assays of tissue oxytocinase activity in the serum. Explanations see Tab. I.

	Condition	No.	a	b	c	d	χ^2	P	Specificity	Sensitivity
single assays	impaired or dead newborn	83	71	12	268	13	8.2064	< 0.01	42.86	14.46
	perinatal mortality	11	8	3	328	25	3.6110	N.S.	10.71	27.27
	low Apgar score	28	25	3	311	25	0.0653	N.S.	10.71	10.71
serial assays	impaired or dead newborn	31	18	13	81	37	0.7408	N.S.	26.00	41.93
	perinatal mortality	7	3	4	96	46	0.8907	N.S.	8.00	57.15
	low Apgar score	7	1	6	98	44	6.6752	< 0.01	12.00	85.71

Tab. III. Prognostic significance of the assays of serum alkaline phosphatase activity. Explanation see Tab. I.

	Condition	No.	a	b	c	d	χ^2	P	Specificity	Sensitivity
single assays	impaired or dead newborn	77	72	5	258	11	0.3342	N.S.	31.25	6.49
	perinatal mortality	11	10	1	320	15	0.0002	N.S.	6.25	9.09
	low Apgar score	27	24	3	306	13	1.4265	N.S.	18.75	11.11
serial assays	impaired or dead newborn	30	22	8	73	31	0.0111	N.S.	20.51	26.67
	perinatal mortality	6	4	2	91	37	0.0513	N.S.	5.13	33.33
	low Apgar score	7	4	3	91	36	0.1564	N.S.	7.69	42.86

Tab. IV. Prognostic significance of the assays of serum heat-stable alkaline phosphatase activity. Explanation see Tab. I.

	Condition	No.	a	b	c	d	χ^2	P	Specificity	Sensitivity
single assays	impaired or dead newborn	77	75	2	264	5	0.0028	N.S.	28.57	2.60
	perinatal mortality	11	11	0	328	7	0.3647	N.S.	0.00	0.00
	low Apgar score	27	26	1	313	6	0.0043	N.S.	14.29	3.70
serial assays	impaired or dead newborn	30	21	9	77	27	0.0424	N.S.	25.00	30.00
	perinatal mortality	6	3	3	95	33	0.7003	N.S.	8.33	50.00
	low Apgar score	7	3	4	95	32	2.0118	N.S.	11.11	57.15

to be prognostic of birth of an impaired infant. Sensitivity of this test is similar to that of P-CAP. The differences in perinatal mortality and low APGAR score in this group are not significant. Falling T-CAP activity was related only to low APGAR score and allows no conclusions concerning impairment of the neonate in general or perinatal mortality. Only one of every four women with falling T-CAP activity gives birth to impaired infants. 42 per cent of the mothers of impaired infants, and 86 per cent of women who gave birth to infants with a low APGAR score, had an abnormal T-CAP profile during pregnancy.

Tabs. III and IV show that neither single nor serial assays of AP and HSAP have value in predicting neonatal impairment. Sensitivity to test was higher for serial assays, and specificity for single ones, similarly to CAP, but lower as a rule than those for both P-CAP and T-CAP.

3 Comments

Until now, evaluation of the enzyme activities under consideration varied. The opinion prevailed that the phosphatases have no prognostic value for predicting the state of the neonate [10, 12, 25, 29,

31]. Only a few authors emphasize that under pathologic conditions, mainly in gestoses and essential hypertension, a sudden rise or fall in HSAP concentration may be prognostically unfavorable [2, 13, 26], and is an indication for strict monitoring rather than for therapeutic decisions [3]. CAP is considered by most authors to be useful in the diagnosis of threatened pregnancy [1, 4, 5, 7, 8, 16, 18, 20, 21, 22, 28], although a few investigators hold the opposite opinion [9]. A special application of this enzyme assay is in the diagnosis of the hypothalamic post-pregnancy syndrome in pregnant women [23], and the combination of CAP with AP and cytohormonal vaginal smears may be of value in the diagnosis of primary and secondary placental insufficiency [30]. The purpose of this study was to compare the prognostic and diagnostic significance of the aforementioned enzyme assays in pregnant women at neuroendocrinological risk. We have not encountered an analysis of this type in the literature and that is why we did not subdivide our material into particular kinds of high-risk pregnancy which only accompanied the neuroendocrinological risk. It was previously found on our material that the arithmetic means of enzyme assays in different months of pregnancy were inversely proportional to the degree of risk to pregnancy [30], but this was not sufficient as a prognostic measure of the magnitude of risk in the event of an abnormal assay result. In view of the above, two criteria of abnormality have been proposed: low values and abnormal profile. Abnormally high values, postulated by some authors for CAP [27, 32] and AP [2, 13, 26], were not taken into account because in our material of pregnancy at neuroendocrinological risk, increased fetal jeopardy was accompanied by decreasing enzyme activities [30]. **The results of the present analysis demonstrated prognostic value of oxytocinase assays in endocrinologically risky pregnancy.** Assays of P-CAP and T-CAP were of almost equal significance, notwithstanding reports of a greater usefulness of P-CAP [6]. **On the other hand, this study confirms that phosphatase assays are of no value prognostically in neuroendocrinologically pathologic pregnancy.** HSAP was not superior to AP, as some authors have claimed. In profile studies based upon arithmetic means, AP was even more useful than HSAP [30], probably owing to the greater dispersion of the values of the latter. We also found that assays of CAP are helpful in the prognosis of perinatal mortality and low APGAR score, i.e. conditions that are frequently encountered in "neuroendocrinological gestosis" [24], the term denoting all neuroendocrinologic disturbance developed during pregnancy, including placental insufficiency, corpus luteum of pregnancy insufficiency etc. However, about a half of future mothers of impaired neonates have values outside the range of these assays. This is understandable in view of the fact that these enzyme activities reflect placental activity but are not directly related to fetal metabolism. In contemporary obstetric diagnostics, they should be supplemented by hormonal assays, especially estriol, examination of amniotic fluid, ultrasonic examinations and others. If this is carried out, unpleasant unexpected situations in the delivery ward and neonatological clinic will be avoided.

Summary

Serum enzyme determinations are now well-established diagnostic tools in so-called "placental insufficiency". A good predictability of oxytocinases (P-CAP-placental oxytocinase and T-CAP-tissue oxytocinase) and a doubtful one of those of phosphatases (AP-alkaline phosphatase, HSAP-heat stable alkaline phosphatase) has been shown in high-risk pregnancies. The purpose of this study was to determine the prognostic value of the above cited enzymes in the so-called "pregnancy at neuroendocrinological risk", i.e. pregnancy in women with a prepregnancy history of hormonal disorders. It was shown that the outcome and results of such pregnancies are poorer that those of normal pregnancies.

The series studied comprised 364 pregnant patients with pregnancy at neuroendocrinological risk that were being monitored by means of serum assays of the four enzymes. An attempt was made to assess each of these enzyme activities both in single (at least one value below 2.5 percentile calculated for healthy subjects) and serial determinations (two consecutive results decreasing or remaining at the same level). Normal and abnormal enzyme results were compared with normal and abnormal conditions of the newborn. **The results presented showed that P-CAP (Tab. I) and T-CAP (Tab. II) levels were useful in prenatal diagnosis of fetal impairment in general,** in addition to perinatal mortality and low values

of the APGAR score. **Neither the single nor serial assays of AP (Tab. III) and HSAP (Tab. IV) were valuable in predicting birth of an impaired neonate.**
Sensitivity of the test, i.e. percentage of women with abnormal enzyme assays among those patients who gave birth to impaired neonates, and specificity of the test, i.e. the percentage of women delivered of impaired neonates among all women with abnormal enzyme assays, of the four enzymes were compared. Sensitivity and specificity of P-CAP and T-CAP were higher than those for AP and HSAP. Moreover, sensitivity for all four enzymes was higher in serial assays, and specificity was higher in single assays.
The results of the present analysis demonstrated the prognostic value of oxytocinase assays also in the pregnancy at neuroendocrinological risk. Assays of P-CAP and T-CAP were of equal significance, notwithstanding reports of a greater usefulness of P-CAP. Assays of CAP were helpful particularly in the conditions on which neuroendocrinological gestosis exerts a direct influence, i.e. in low Apgar score and perinatal mortality. On the other hand, serum alkaline phosphatases proved useless in endocrine pathology of pregnancy and HSAP was not superior to AP.
About one half of future mothers of impaired neonates had enzyme results outside the range of the assays under consideration. This could be explained by the fact that these enzymes activities reflect placental function and are not directly related to fetal metabolism. Because of that they should be supplemented by other diagnostic methods being used in a clinic of high-risk pregnancy.

Keywords: APGAR score, high-risk pregnancy, perinatal mortality, placental insufficiency, pregnancy at neuroendocrinological risk, serum alkaline phosphatase, serum heat-stable alkaline phosphatase, serum placental cystine aminopeptidase, serum tissue cystine aminopeptidase

Zusammenfassung

Vergleich des prognostischen Wertes der plazentaren und Gewebs-Oxytocinase sowie der alkalischen Phosphatase und ihrer hitzestabilen Fraktion im Serum von Schwangeren mit neuroendokrinologischem fetalem Risiko
Serumenzymbestimmungen gehören heutzutage zum eingeführten diagnostischen Instrumentarium bei der sogenannten plazentaren Insuffizienz. Gute Voraussagekraft konnte diesbezüglich bei Risikoschwangerschaften für die Oxytocinase (P-CAP plazentare Oxytocinase und T-CAP Gewebsoxytocinase) und zweifelhafte Aussagekraft für die Phosphatasen (AP = alkalische Phosphatase, HSAP = hitzestabile alkalische Phosphatase) nachgewiesen werden. Ziel dieser Studie war es, den prognostischen Wert der angesprochenen Enzyme bei Schwangerschaften mit sogenanntem neuroendokrinologischem Risiko nachzuweisen. Dabei handelt es sich um Schwangerschaften bei Frauen mit einer präpartalen Anamnese von Hormonstörungen. Es konnte gezeigt werden, daß der fetale Ausgang bei solchen Schwangerschaften ungünstiger ist als bei normalen Graviditäten.
Die Serie bestand aus 364 schwangeren Frauen mit neuroendokrinologischen Risikoschwangerschaften, die durch die Bestimmung der vier Enzyme überwacht wurden. Es wurde der Versuch unternommen, jede dieser Enzymaktivitäten sowohl in Einfach- (mindestens ein Wert unterhalb der 2,5ten Perzentile bezogen auf gesunde Individuen), sowie in Serienbestimmungen (zwei aufeinanderfolgende Meßresultate, die abfallen oder auf derselben Höhe verbleiben) zu bestimmen. Normale und abnorme Enzymmeßresultate wurden mit unauffälligen sowie auffälligen Befunden beim Neugeborenen verglichen. **Die vorgelegten Resultate zeigen, daß die P-CAP (Tab. I) und T-CAP (Tab. II) -Spiegel nützlich waren in der pränatalen Diagnostik einer generellen fetalen Beeinträchtigung** unabhängig von der perinatalen Mortalität und von tiefen APGAR-Zahlen. **Weder die Einzel- noch die Serienbestimmungen der alkalischen Phosphatase (Tab. III), sowie der hitzestabilen alkalischen Phosphatase (Tab. IV) waren für die Voraussage eines in seinem Zustand beeinträchtigten Neugeborenen brauchbar.** Die Sensitivität und die Spezifizität des Testes wurde für alle vier Enzyme miteinander verglichen, d.h., der Prozentsatz an Frauen mit nicht normalen Enzymwerten unter jenen Patientinnen, die ein geschädigtes Kind geboren hatten und der Prozentsatz an Frauen, die ein geschädigtes Neugeborenes hatten innerhalb der Gruppe von Patientinnen, die alle abnormale Enzymwerte aufwiesen. Die Sensitivität und Spezifität der P-CAP und T-CAP war durchweg höher als jene der AP und HSAP. Darüberhinaus zeigte sich, daß die Sensitivität für alle vier Enzyme bei Serienbestimmungen höher war, wo hingegen die Spezifität bei Einzelbestimmungen höher lag. Die Ergebnisse der vorliegenden Analyse belegen den prognostischen Wert der Oxytocinasebestimmung auch bei Schwangerschaften mit neuroendokrinologischem Risiko. Die Bestimmung der P-CAP und T-CAP war von gleichwertiger Aussagekraft, was Berichten widerspricht, die von größerer Brauchbarkeit der P-CAP berichten. Die Bestimmung der P-CAP war besonders in jenen Situationen hilfreich, bei welchen eine neuroendokrinologische Gestose einen direkten Einfluß ausübte, d.h., bei tiefen Apgarzahlen und perinataler Mortalität. Andererseits zeigte sich die alkalische Serumphosphatase wenig geeignet beim Vorliegen von endokrinologischer Schwangerschaftspathologie und die HSAP war der AP diesbezüglich nicht überlegen. Ungefähr die Hälfte der werdenden Mütter mit geschädigten Neonaten wiesen Enzymmeßwerte außerhalb der Streubreite für die jeweilige Enzymbestimmung auf. Dies konnte durch die Tatsache erklärt werden, daß diese Enzymaktivitäten die plazentare Funktion widerspiegeln und nicht direkt mit dem fetalen Metabolismus zusammenhängen. Aus diesem Grunde sollten diese Bestimmungen durch andere diagnostische Methoden ergänzt werden, die in der Klinik, die Schwangerschaften betreut, zur Anwendung kommen.

Schlüsselwörter: APGAR-Score, alkalische Serumphosphatase, Fetus, Gewebs-Cystine Aminopeptidase, hitzestabile Serumphosphatase, perinatale Mortalität, Plazentainsuffizienz, plazentare Cystin-Aminopeptidase, Risikoschwangerschaft, Schwangerschaft mit neuroendokrinologischem Risiko.

Résumé

Valeur comparative de pronostic du sérum-oxytocinase placentaire et tissulaire, de la phosphatase alcaline et de sa fraction stable à la chaleur dans les grossesses avec risque neuroendocrinologique

Les évaluations d'enzymes du sérum sont à présent des moyens éprouvés pour le diagnostic de ladite «insuffisance placentaire». Une bonne prédiction d'oxytocinases (P-CAP-oxytocinase placentaire et T-CAP-oxytocinase du tissu) et une douteuse de celles de phosphatases (AP-phosphatase alcaline, HSAP-phosphatase alcaline stable à la chaleur) ont été prouvées pour les grossesses avec un degré élevé de risque. Cette étude a pour but d'illustrer la valeur de pronostic des enzymes cités ci-dessus dans ladite «grossesse à risque neuroendocrinologique», c.à.d. celle de femmes ayant eu des troubles hormonaux avant le début de leur grossesse. On a vu que l'issue et les résultats de telles grossesses sont moins bons que ceux des grossesses normales.

Les séries examinées ont porté sur 364 femmes enceintes à grossesse avec risque neuroendocrinologique qui ont été contrôlées au moyen de sérotests des quatre enzymes. On a essayé d'évaluer chacune de ces enzyme-activités à la fois en déterminations simples (au moins une valeur au-dessous de 2,5 pour cent calculée pour les sujets sains) et sérielles (deux résultats consécutifs en baisse ou restant au même niveau). Puis on a comparé les enzyme-résultats normaux et anormaux aux conditions normales et anormales des nouveaux-nés.

Les résultats présentés ont montré que les niveaux P-CAP (Tab. I) et T-CAP (Tab. II) sont utiles pour le diagnostic prénatal de troubles foetaux d.une façon générale, outre la mortalité périnatale et les valeurs basses du score APGAR. **Ni les essais simples, ni ceux en série de AP (Tab. III) et HSAP (Tab. IV) n'ont été valables pour faire prévoir la naissance d'un nouveau-né en mauvaise condition.**

On a comparé la sensitivé du test des quatre enzymes, c.à.d. le pourcentage des femmes aux enzyme-tests anormaux parmi les parturientes ayant donné naissance à des nouveauxnés en mauvais état de santé, et la spécificité du test, c.à.d. le pourcentage des femmes ayant accouché des nouveaux-nés non sains parmi toutes les femmes aux enzyme-tests anormaux. La sensitivité et la spécificité de P-CAP et de T-CAP ont été plus élevés que celles de AP et de HSAP. De plus, la sensitivité pour les quatre enzymes a été plus élevée dans les essais en série, et la spécificité plus élevée dans les essais simples.

Les résultats de l'analyse présente ont démontré la valeur de pronostic des essais d'oxytocinase aussi dans la grossesse avec risque neuroendocrinologique. Les essais de P-CAP et de T-CAP ont été d'égale signification, malgré les rapports d'une plus grande utilité de P-CAP. Les tests de CAP ont été particulièrement utiles pour illustrer les sonditions dans lesquelles la gestose neuroendocrinologique exerce une influence directe, c.à.d. dans un score Apgar bas et la mortalité périnatale. D'autre part, les sérum-phosphatases alcalines se sont révélées inutiles dans la pathologie endocrinienne de grossesse et HSAP n'a pas été supérieure à AP. A peu près la moitié des futures mères de nouveaux-nés non sains ont eu des enzyme-résultats en dehors de la zone des essais considéerés, ce qui a pu s'expliquer du fait que ces enzyme-activités reflètent la fonction placentaire et ne sont pas directement reliées au métabolisme foetal. A cause de cela il conviendrait de les compléter par d'autres méthodes de diagnostic utilisées dans un hôpital où sont soignées beaucoup de grossesses avec un degré élevé de risque.

Mots-clés: Score APGAR, foetus, grossesse avec risque neuroendocrinologique, grossesse avec un degré élevé de risque, insuffisance placentaire, mortalité périnatale, sérum-aminopeptidase cystine placentaire, sérum-aminopeptidase cystine tissulaire, sérum-phosphatase alcaline, sérum-phosphatase alcaline stable à la chaleur.

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Received May 27, 1975. Accepted June 14, 1976.

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